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The Clinical Aspects, Diagnosis and Epidemiology of Histoplasmosis

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The deep-seated forms of fungus-diseases with involvement of the internal organs are very diverse in their clinical manifestations. They should be kept in mind in the differential diagnosis of every unexplained infectious disease, and above all in that of tuberculosis. Therefore all doctors, and not just a small number of specialists, should be familiar with them. Meanwhile, if such fungal infections as deep-seated blastomycosis or actinomycosis are still being disregarded in differential diagnosis, then it is certain that histoplasmosis and coccidioidomycosis will be undetected by doctors.

In our present work we set for ourselves the goal to conduct a brief review of the literature about one of the deep mycoses that is not described in our literature. Although not a single case of this severe disease has been described in our country we cannot be certain that this mycosis has not gone undetected. Histoplasmosis was first described by Darling in 1906 in the Panama Canal Zone. For a long time it was considered that this disease was encountered very rarely and only in tropical countries, therefore it seemed of small importance. In 1926, however, Watson and Riley described the first case of histoplasmosis in the U. S. A. In 1938 there were 138 observations in the world literature. Of these, four-fifths were evidenced in the U. S. A., and the rest in Mexico, South and Central America, Canada, Australia, Austria, Spain, Holland, Portugal, Turkey, and Bulgaria.

Histoplasmosis in adults can have an acute, subacute, or chronic course. In children, particularly in the early ages, the disease has an acute character. All of the organs and tissues of the organism and above all the reticuloendothelial system can be afflicted in this disease. In connection with this its clinical manifestations are extremely varied. Generalized histoplasmosis is accompanied by an irregular type fever, splenohepatomegaly, anemia, lymphadenopathy, and sharp emaciation.

Dailey deems that the bones and cartilages are unaffected by histoplasmosis because they contain no lymphoid tissues. Nevertheless, single cases of bone affliction have been described. Pashev, Rimanevskiy and Markovskiy described a case in Bulgaria of a four year old child with bone histoplasmosis.

**PULMONARY HISTOPLASMOSIS.** In 1908, during an autopsy, Darling discovered small nodules, eight millimeters in diameter, situated beneath the pleura in the lungs of a generalized histoplasmosis patient. It is now considered probable that an affliction of the lungs in the form of acutely elapsing infiltrates or multiple minute nodules situated beneath the pleura is almost always found in generalized histoplasmosis. This also explains the pains in the breast, of which the patients usually complain. Gass, Harrison, Puffer, Stewart and Williams were the first to notice that a series of patients in Tennessee had calcified foci in the lungs with negative reactions to tuberculin. In 1954, Christie and Peterson, and also Palmer and his coworkers, announced that patients with calcified foci in the lungs gave positive reactions to histoplasmin. Because these patients were living in areas endemic to histoplasmosis, the conclusion was drawn that there exist a benign form of pulmonary histoplasmosis in addition to the generalized acutely elapsing form. Furcolow, in his investigation of school children in Kansas, detected miliary and nodular lesions in their lungs. A high sensitivity to histoplasmin was also noted in these patients. Further observations showed that within 2-4 years these lesions calcified, but the skin test with histoplasmin remained persistently positive. Furcolow was able to isolate Histoplasma capsulatum from gastric washings from a four year old child, and was thus able to prove a positive relation between these lesions and histoplasmosis.

Now, the existence of a benign form of pulmonary histoplasmosis is considered as firmly established. Only a few of the patients complain of a cough, difficulty in breathing, pains in the breast, and blood spitting; sometimes night sweats are noted. A great number of the patients have no complaints and the disease is only accidentally detected in x-ray examination.

The x-ray picture in histoplasmosis is characterized by multiple infiltrates or minute foci disseminated over both of the lung fields. The broncho-pulmonary lymphatic nodes are almost always enlarged; sometimes they attain such dimensions that primary tuberculosis or lymphoblastoma are suspected. Now and then the primary manifestations of histoplasmosis are limited to one or two foci in the lungs. In such cases it is impossible to distinguish this affliction from that of tuberculosis.

Eventually some of the infiltrates disappear and others are calcified. The broncho-pulmonary lymphatic nodes are also subject to calcification. Three to five years are required for calcification of the foci of affliction, although Christie has observed calcified foci in the lungs of a four month old baby that had died as a result of generalized histoplasmosis.

Badenhopf writes that the lungs are very often affected in histoplasmosis, and that more than one-fourth of the adult patients have calcifications. Together with this infiltrates are observed, at times with caverns. In contrast to tuberculosis, in which the lung segment situated closer to the apex is afflicted, the

infiltrates in histoplasmosis are encountered in various segments of the lungs. Mediastinal adenopathy is more frequently encountered in histoplasmosis than in tuberculosis.

Arblaster, too, points out that the basic sign of pulmonary histoplasmosis is the presence of calcified foci of a round or oval form with a diameter from 0.25 to 1.5 centimeters. Histoplasmosis produces significantly more enlarged lesions in the lungs than other diseases.

The positive skin reaction to histoplasmin is of great importance for differential diagnosis.

On the basis of personal observations and a review of the literature Hodgson, Weed and Clagett come to a conclusion that pulmonary histoplasmosis does not have a characteristic clinical picture that could distinguish it from tuberculosis and other lung diseases. In diagnosis, particular attention must be given to an investigation directed toward the exposure of Histoplasma capsulatum in the sputum, the bronchial secretion, the stomach contents, and the pleural fluid. Johnson and McGurdy, however, believe that a diagnosis of pulmonary histoplasmosis should be made even in the cases where the pathogen cannot be isolated. Presence of calcified foci, a positive reaction to histoplasmin, and data about the patient being in an endemic hearth will assist in establishing a diagnosis.

Crofton cites two observations of probable pulmonary histoplasmosis: One of the patients, 45 years old, complained of a dry cough that had been bothering him in the mornings. Pulmonary emphysema and enlarged lymphatic nodes in the axillary region and on the posterior cheek surface were detected in the examination of the patient. A roentgenogram showed the presence of calcified foci, 2-3 millimeters in diameter, which were diffused through both lung fields. At first glance at the roentgenogram it was possible to think of tuberculosis. The wide dissemination and the symmetry of the affliction are not common for this disease. The intracutaneous test with histoplasmin proved positive. It was learned from the anamnesis that the patient had been in an endemic hearth. All of this forces the author to presume pulmonary histoplasmosis.

Puckett informs of 22 patients with limited foci of affliction in the lungs. These foci were exposed in x-ray examinations. No changes could be detected through percussion and auscultation in the overwhelming majority of the patients. In the author's opinion this is explained by the foci being too minute, and because a large portion of them were in inactive condition. At first, tuberculosis was presumed in nine of the patients, and antituberculosis therapy was conducted for a period of 120 days. In follow-up x-ray investigations there were no changes evidenced as a result of the treatment that had been conducted. Resection of the afflicted lung segments was made in all 22 patients. Histoplasma capsulatum was detected in the histological and bacteriological investigations.

The data of Meleney, who described a group of patients that suffered tuberculosis and pulmonary histoplasmosis simultaneously, are worthy of mention.

**HISTOPLASMOSIS OF THE GASTROINTESTINAL TRACT.** Darling discovered an affliction of the small and large intestines in an autopsy of two patients with generalized histoplasmosis. Other authors also describe changes, which are discovered in autopsy, in the region of the digestive tract.

Ulcerations and granulomatous lesions of the mouth, pharynx, and oral region are noted in a significant number of patients with generalized histoplasmosis.

Fitzpatrick and Neiman observed a patient with generalized histoplasmosis who had died from a gastric ulcer accompanied with profuse bleeding.

Baferly, Trafas, McClure, Christopherson, Miller, Kotcher et al. isolated Histoplasma capsulatum from a process of the cecum in appendicitis.

Shall, of the Vanderbilt University Hospital, informs of 37 patients with generalized histoplasmosis. In 28 of the patients the illness was accompanied by nausea, vomiting, pains in the abdominal region, diarrhea with blood, jaundice, and enlargement of the liver and spleen.

With proctoscopy and sigmoidoscopy multiple polypoid formations, from eight to ten millimeters in diameter, were detected. They were ulcerated and bleeding readily. A great quantity of macrophages, containing Histoplasma capsulatum, were discovered in the discharge from the ulcers and in the tissue taken in biopsy. A culture of the fungus was isolated from the bone marrow, from the blood, and from the bowel movements of these patients. The disease resulted in the death of 32 of the patients. Involvement of the bone marrow, lungs, and intestine was discovered in the autopsy. The mucous membrane of the intestine proved to be covered with multiple nodules of a yellowish-red color and from 5 to 200 millimeters in diameter. Many of them were ulcerated. Macrophages containing Histoplasma capsulatum were discovered in the discharge from the ulcers. Elements of the fungus were also discovered in large numbers in the livers Kupffer's cells and in the connective tissue surrounding the gall bladder.

An affliction of the intestine is particularly often noted in histoplasmosis of children, in whom the illness is accompanied by intestinal disorders, diarrhea and expressed splenomegaly. In autopsy one finds an involvement of the intestine's lymphoid tissue and the mesenteric nodes, which are often ulcerated. Basically, these are the clinical symptoms of histoplasmosis.

A great significance for the diagnosis of this disease is held by the positive reaction to histoplasmin, which is a broth filtrate of a culture of Histoplasma capsulatum, or an extract from its yeast phase. In 1949, Edward showed that 0.1 milliliter of standard histoplasmin in a dilution of 1:1,000 gives a positive reaction in persons infected with histoplasmosis. The result is noted after 24-48 and 72 hours. Of lesser importance for the diagnosis are the complement fixation test and the agglutination test.

**MYCOLOGICAL DIAGNOSIS.** In 1906, Darling, having described the first observations of histoplasmosis, believed that he had succeeded in exposing a new protozoal disease. For a period of three decades the diagnosis of this disease was established only with the appearance of the parasites in the affected tissue.

Not until 1934 was DeMonbreun able to produce a culture from the blood and spleen of a five month old baby with histoplasmosis. Whereupon it was proved that the fungus grows on common nutrient media and does not require special conditions for existence. The pathogen can be detected in specimens of bone marrow, in the liver and in the other organs, in the peripheral blood, in the pleural exudate, in the sputum, in gastric lavage waters, in stomach contents, in bowel movements, in discharge from ulcers, and in tissues taken by biopsy. Winkel and his coworkers detected Histoplasma capsulatum in biopsy specimens from the uterine mucosa of women suffering disorders of the menstrual cycle, and living in endemic hearths.

Investigation of primary material is made in smears stained by the Wright method, by hematoxylin-eosin, by the Romanovsky-Giemsa method, or by the McManus method.

Puckett believes that the usual staining methods are applicable only with disseminated histoplasmosis, when there are many parasites. The small number of fungal elements in localized histoplasmosis can be overlooked in such a staining. The author recommends staining the preparations according to McManus.

In microscopic investigations of native material and mainly of stained smears, one observes oval bodies, 1-5 microns in size, situated most frequently intracellularly. Budding forms are also encountered. Similar oval bodies, which are situated in the cytoplasm of macrophages, are discovered in histological examination of tissue taken by biopsy. In a few cases one encounters a mycelium of the fungus. The fungus grows on meat broth with glucose, on agar with blood and dextrose, and on other nutrient media. Cultivation at 37°C leads to a yeast growth, while at room temperature a mycelium can also be produced while cultivating the fungus at 37°C on a liquid medium.

On agar with blood, at 37°C, the fungus forms a moist white colony covered with deep radial grooves. In microscopic investigation one discovers minute cells, 1 to 5 microns in diameter, of oval form with a thick capsule and budding in places.

On Sabouraud's culture medium with glucose, and at room temperature, the fungus grows slowly. Growth does not start until the 7th-8th day. White villous colonies appear that are analogous with the pleomorphic colonies of the dermatophytes. Later, the culture darkens and acquires a brown tint. In microscopic investigation one detects a branching septate mycelium with small round or pear shaped spores, approximately 2.5-3 microns in diameter, which sit directly on the hyphae, or are attached to them by short sterigmata. Together with these in the culture are the thin septate, rocket-shaped at times, filaments of the mycelium. With such an appearance the culture can be mistaken for a culture of Blastomyces dermatitidis. The presence of serrate chlamydospores, from 10 to 20 microns in diameter, which are characteristic for Histoplasma capsulatum, resolves this problem. These chlamydospores do not appear until 2-3 weeks after the development of growth, and they have a great diagnostic importance. In addition, a culture of Histoplasma capsulatum grows much slower than Blastomyces dermatitidis. Therefore it is necessary to observe a seeding of material for Histoplasma capsulatum for a protracted period, and it should be considered negative only after the lapse of a month.

For purposes of diagnosis, the infected material and cultures are intraperitoneally inoculated into young animals - guinea pigs, mice, rabbits, and the other laboratory animals. Thereupon Histoplasma capsulatum causes an affliction of the internal organs, where it is possible to detect the pathogen in histological, bacteriological, and bacterioscopic investigations.

**EPIDEMIOLOGY OF HISTOPLASMOSIS.** The fungus Histoplasma capsulatum penetrates into the organism primarily via the respiratory route. This is indicated by the large number of observations of primary histoplasmosis of the lungs. Evidently the digestive tract can also play the role of an entrance portal, mainly in children.

It is evident from the survey by Curtes and Grekin that a significant portion of the illnesses with progressive histoplasmosis begins with lesions of the skin and mucous membranes.

The soil is considered to be the basic reservoir of this fungal infection. Hamons was the first to isolate Histoplasma capsulatum from the soil, and to prove that this fungus is a saprophyte living freely in the soil. In view of the difficulty in isolating the fungus directly from the soil he proposed to inoculate mice with a suspension of soil in physiological solution and later to isolate a culture of the fungus from the liver or spleen of these animals.

Later on, Furcolow, Larsh, Zeidberg, and Agello also isolated this fungus from the soil from yards and chiefly from chicken coops in the endemic hearths of histoplasmosis. It is presumed that the fungus spores are spread by the wind, and that the infection of humans and animals occurs by the exogenic route, through the air. Furcolow, Mengess, Larsh, and others isolated Histoplasma capsulatum from the internal organs, chiefly from the liver, spleen, and lymphatic glands, of dogs, cats, rats, mice, and other rodents. Positive reactions to intracutaneous injections of histoplasmin were received in cattle in the endemic hearths of Kansas and Missouri. Regardless of the close contact between man and his domestic animals, attempts to prove the possibility of man becoming infected from animals have proven unsuccessful. Cases of illness of several members of the same family have been described, but nevertheless the possibility of transmittal of the infection from person to person has never been proved. Still, in laboratory personnel who have worked with Histoplasma capsulatum cultures the reaction to histoplasmin will change from negative to positive. In single cases the infection takes the asymptomatic form, in others affliction of the respiratory tract is evidenced in x-ray examination. Thus, regardless of the large number of works that have been conducted during the past ten years in this area, the epidemiology of histoplasmosis is to date insufficiently clear.

**TREATMENT.** There is no specific treatment for histoplasmosis. Preparations of iodine, heavy metals, neocarsphenamine, sulfanilamides, and liver extracts are used. Seabery proved that stilbamidine arrests the growth of Histoplasma capsulatum. Both he and other authors, however, received poor results in the treatment of histoplasmosis patients with this preparation. Christie and coworkers received good results by using ethylvanilate. In focal histoplasmosis, resection of the focus has proven successful.

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